Science & Technology REVIEW

April 2001

U.S. Department of Energy's
Lawrence Livermore
National Laboratory

Simulations Push the Boundaries of Bioscience

Also in this issue:

- **Diamond Machining on the Grand Scale**
- **Collaborating to Defeat Cancer**
- **RAMping Up Computer Performance**

About the Cover

Using the Laboratory's terascale supercomputers, computational biologists are developing advanced simulations that reveal in unprecedented detail the mechanisms of biological processes. On the cover is one of these simulations—the anticancer drug cyclophosphamide (in green) forming a cross-link to DNA. This cross-linking is thought to be key to the drug's anticancer capability. The article beginning on p. 4 reports on this and other computational biological work that links advanced simulations with laboratory experiments and puts Livermore at the forefront of this new approach to biological research.

Cover design: Lew Reed

About the Review

Lawrence Livermore National Laboratory is operated by the University of California for the Department of Energy. At Livermore, we focus science and technology on assuring our nation's security. We also apply that expertise to solve other important national problems in energy, bioscience, and the environment. *Science & Technology Review* is published 10 times a year to communicate, to a broad audience, the Laboratory's scientific and technological accomplishments in fulfilling its primary missions. The publication's goal is to help readers understand these accomplishments and appreciate their value to the individual citizen, the nation, and the world.

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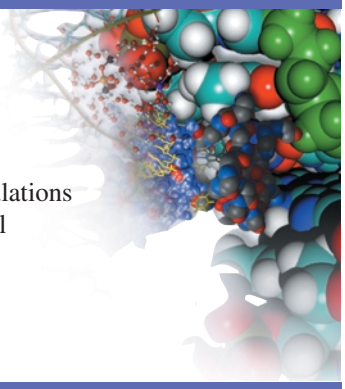

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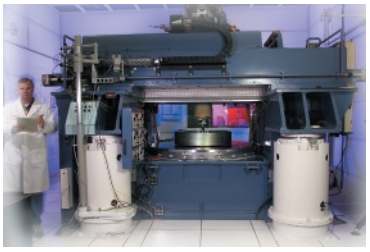

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Laser stroke treatment proven safe

The Endovascular Photo-Acoustic Recanalization (EPAR) laser system used to break up blood clots in the brain has been shown to be safe as a new treatment for stroke. The EPAR system, which is made by Endovasix Corp. of Belmont, California, was originally created by scientists at Lawrence Livermore in cooperation with Endovasix.

The device works by delivering laser energy in the form of an acoustic wave into a blood clot that is blocking the flow of blood in the brain. The laser beam reaches to the site of the clot via a catheter threaded through the body's blood veins.

EPAR was tested in a recently completed study involving 26 patients with severe stroke. The device was shown to be safe and to produce no major complications. Dr. Helmi L. Lutsep of the Oregon Stroke Center in Portland, Oregon, reported the finding of the safety study at the 26th International Stroke Conference of the American Heart Association in Fort Lauderdale, Florida. Lutsep also indicated that a multicenter trial of the laser treatment system's efficacy will begin soon.

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Lab forensic work aids in arrest of "Angel of Death"

The Laboratory's Forensic Science Center and its director Brian Andresen were instrumental in the recent rearrest of Efren Saldivar, the self-proclaimed "Angel of Death" and alleged killer of terminally ill patients at a Glendale, California, hospital.

Special analyses by the center gave Glendale investigators evidence they could use to arrest Saldivar and charge him with the murders of six patients. Saldivar, a former respiratory therapist at Glendale Adventist Medical Center, was first arrested in 1998. He confessed to killing between 100 and 200 patients, whom he deemed "ready to die," by injecting two paralyzing drugs, Pavulon and succinylcholine chloride, into the patients' IVs. He later recanted and was released.

At the request of Michael Peat, then president of the American Academy of Forensic Sciences, Andresen traveled to southern California to assist in the autopsies of the exhumed remains of some of the "most mysterious" of the Glendale deaths. He prepared and demonstrated the proper sampling equipment for coroner's office personnel and, using a new scientific protocol, showed them how to retrieve and preserve evidence correctly.

Because succinylcholine chloride breaks down quickly into chemicals normally found in human tissue, Andresen concentrated on Pavulon, a potent, synthetic muscle relaxant often administered in low doses to patients on artificial respirators. He found 6 positive results for Pavulon out of 20 autopsies.

In early January, Saldivar was rearrested, based primarily on Andresen's findings.

For more information on Livermore's Forensic Science Center, its accomplishments, and mission, visit the Web site at http://www.llnl.gov/IPandC/op96/10/10h-for.html.

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Lab physicists' revised theory of nebula formation

Scientists may be closer to understanding the formation of the famous Eagle Nebula, thanks to the recent simulations of Livermore physicists Jave Kane, Dmitri Ryutov, and Bruce Remington.

The nebula is located about 5,700 light years from Earth and is known for its spectacular Pillars of Creation, gaseous clouds towering over 9 trillion kilometers tall. The nebula became well known after the Hubble Space Telescope captured a dramatic image of the pillars in 1995.

Between 1995 and 1998, scientists believed the pillars to be a classic example of a Rayleigh–Taylor instability, which occurs when a light material supports a dense one in a gravitational field, as, for example, when a light salad oil is trying to support a layer of relatively dense vinegar. The dense material will fall in spikes into the lighter material, which in turn rises in bubbles into the denser material, until the fluids change places.

In 1998, however, Marc Pound of the University of Maryland used the Berkeley–Illinois–Maryland Array in Hat Creek, California, to measure the velocity and density of the gas in the pillars. He found them inconsistent with the measurements required to support the Rayleigh–Taylor explanation of the pillars.

The Livermore simulations reconcile Pound's measurements and the Rayleigh–Taylor explanation. Specifically, intense ultraviolet light from nearby stars heats and evaporates the surface layer of the Eagle Nebula, a gaseous cloud composed mostly of hydrogen and helium. The hot evaporated gas accelerates the cold, dense cloud. However, because it continues to be pulled gravitationally toward the hot evaporated gas, the accelerating cloud is Rayleigh–Taylor unstable.

The new theory considers possible variations in the stellar flux irradiating the clouds and in the finite cloud thickness. Finally, unlike the Rayleigh–Taylor model, which assumes incompressible matter, the new model takes into account the compressibility of heated gases.

The next step is to take the revised theory from simulation to experiments using the Omega laser at the University of Rochester in New York.

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Computer Modeling Advances Bioscience

BIOLOGICAL scientists are beginning to reap the benefits of integrating high-performance computing with laboratory research. Work in Lawrence Livermore's Biology and Biotechnology Research Program is bringing computer modeling into the same essential role in bioscience that it plays in physics and engineering. Every complex physics experiment uses computer models to help design the experiment, guide its construction, predict the outcome, and suggest modifications. Every large engineering project, such as building an automobile, bridge, or integrated circuit, uses computational modeling to explore alternatives, optimize designs, and recognize flaws.

Over the past century, bioscience has evolved from a qualitative, observational discipline to a quantitative, predictive science. Molecular biology and genetics are generating vast amounts of complex data, and the generation rate is accelerating. Given the amount of information, more and more bioscientists recognize the need for large-scale computational tools. At the least, researchers need computers to collect, store, organize, and display their data and increasingly are using computers to accurately model the complex processes they are studying.

Throughout its history, the Laboratory has pioneered the use of powerful computers to solve complex scientific problems. The best known example is the extraordinarily complex modeling of nuclear detonations. At first glance, modeling nuclear weapons and modeling biological processes would seem to have little, if anything, in common. In truth, they are surprisingly similar. In both, many complex processes and variables work together to produce an end result with only a few measurable quantities, which are often averages spanning the entire experiment. Diagnostics are few—many of the most interesting quantities cannot be observed directly or take place on extremely brief time scales. Individual experiments are expensive and/or time consuming, so only a few can be conducted—not nearly enough to explore all the alternatives.

Modeling has many values. It fills the gaps in sparse experimental data, gives researchers insights into intermediate processes that cannot be directly observed, and allows many more virtual computer experiments than actual physical experiments. Computer models also force scientists to make sense of all available data at once, not just in piecemeal fashion. By integrating disparate bits of data, models inevitably provide insight into a problem.

As described in the article starting on p. 4, advanced computation permits bioscientists to really "see" inside biochemical processes in breathtaking detail and learn how reactions take place. Modeling occurs at several levels of resolution. It can simulate the behavior of a few hundred atoms—for example, a few base pairs of DNA—with full quantum mechanical resolution. Or it can reveal the workings of larger systems with more abstraction and less precision. For example, the three-dimensional folding of a long chain of amino acids into a working protein is modeled partly from its physical and chemical properties and partly by comparing the sequence with known "folds"—structural patterns that are components of other functional proteins.

As in the physical and engineering sciences, confidence in biochemical computational models is developed by constantly testing them against experimental data obtained by biologists and biochemists working closely with computational experts. As the models are found to accurately predict measurable quantities, they begin to be trusted and relied on to guide experiments and to raise questions that suggest productive new lines of research.

Today, Lawrence Livermore scientists are at the forefront of integrating computation and experiment in bioscience. The challenge is to improve modeling accuracy and extend biosimulations to higher levels of complexity—for example, to groups of proteins working together to repair damaged DNA and, beyond, to intracellular components, structures, and communication paths. These research dreams extend to someday modeling the workings of an entire cell. The quest will, indeed, be an exciting one.

■ Bert Weinstein is acting Associate Director, Biology and Biotechnology Research Program.

A New Kind of Biological

Advanced simulations are revealing the exact mechanisms of key biological processes.

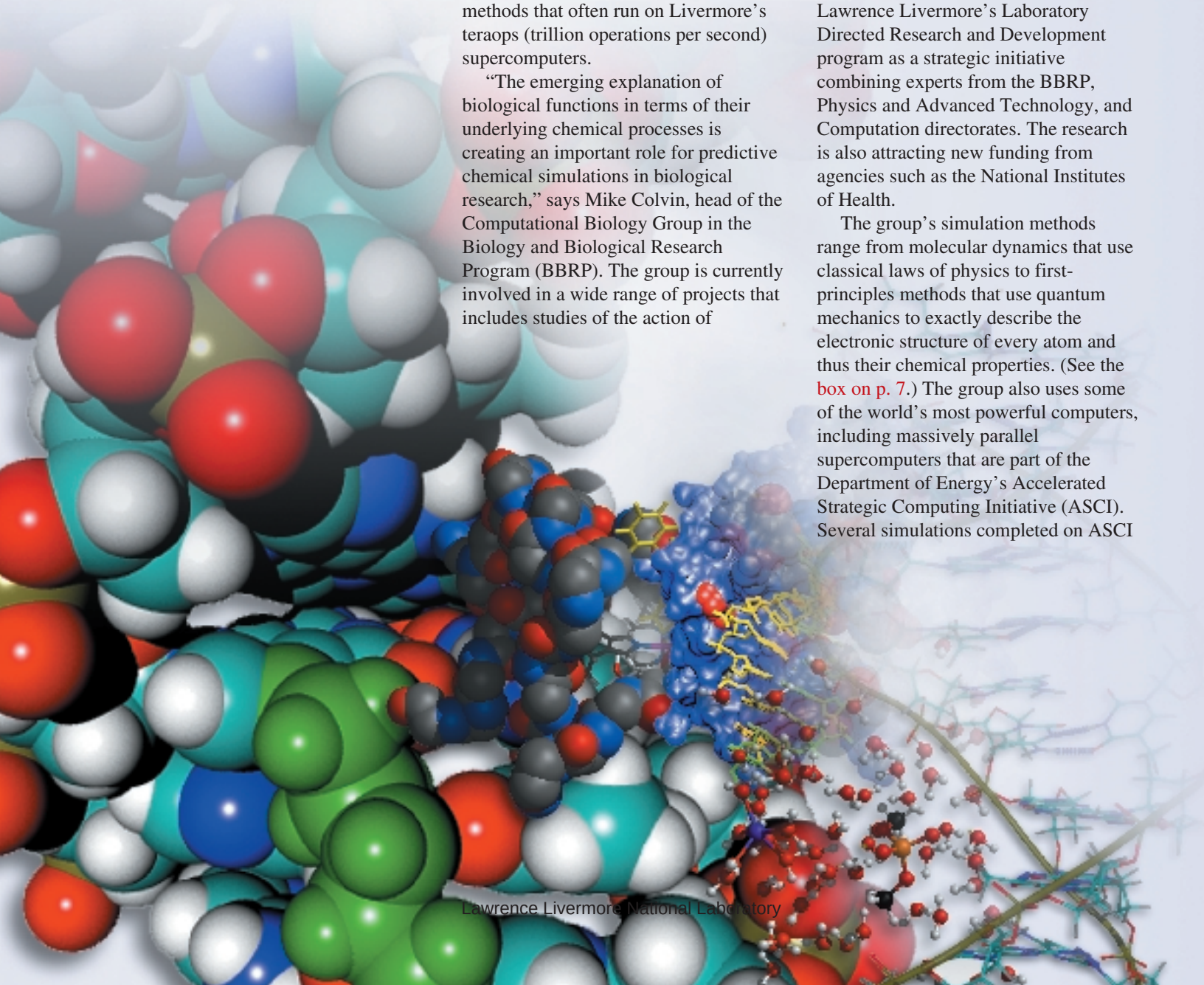
A team of Lawrence Livermore researchers is developing a new approach to biological research by linking advanced simulations with laboratory experiments to explain biological phenomena at an unprecedented level of detail. In addition to promoting close collaborations with other biological scientists at the Laboratory, the research involves newly developed simulation methods that often run on Livermore's teraops (trillion operations per second) supercomputers.

"The emerging explanation of biological functions in terms of their underlying chemical processes is creating an important role for predictive chemical simulations in biological research," says Mike Colvin, head of the Computational Biology Group in the Biology and Biological Research Program (BBRP). The group is currently involved in a wide range of projects that includes studies of the action of anticancer drugs, the DNA-binding properties of mutagens in food, the mechanisms of DNA repair enzymes, and the biophysics of DNA base pairing.

All of the projects strongly tie modelers to experimental researchers in BBRP because, says Colvin, "There is a growing consensus that the integration of computation and experiment will accelerate progress in biology."

The work is funded in part by Lawrence Livermore's Laboratory Directed Research and Development program as a strategic initiative combining experts from the BBRP, Physics and Advanced Technology, and Computation directorates. The research is also attracting new funding from agencies such as the National Institutes of Health.

The group's simulation methods range from molecular dynamics that use classical laws of physics to first-principles methods that use quantum mechanics to exactly describe the electronic structure of every atom and thus their chemical properties. (See the box on p. 7.) The group also uses some of the world's most powerful computers, including massively parallel supercomputers that are part of the Department of Energy's Accelerated Strategic Computing Initiative (ASCI). Several simulations completed on ASCI



Lawrence Livermore National Laboratory

Research

computers have established new standards for size and accuracy in the chemical modeling of biological processes.

DNA Lesions Need Repair

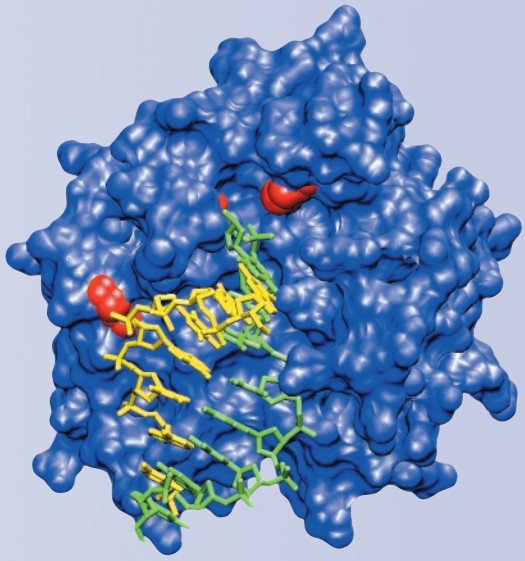
Much of the computational biology work focuses on the dynamics and structure of DNA and repair mechanisms for specific forms of DNA damage. Human genes are made up of long, double-stranded DNA molecules that contain the instructions for building the proteins that make up the machinery of every cell. Understanding the role of DNA repair and other processes that protect cells from radiation and chemical insults has been a long-term interest at Lawrence Livermore.

One simulation project has shown how human repair enzymes recognize a common form of DNA damage called an abasic lesion. These lesions occur when a stretch of DNA loses one of its constituent bases, leaving a gap in the chain. Such lesions arise spontaneously more than 10,000 times per day in every cell. They can also be caused by exposure to pesticides, food mutagens, and ionizing radiation from the sun. If unrepaired, the damage can lead to disease, notably cancer, through a mutation in the genetic code.

Cells have a set of repair enzymes (proteins) that scan DNA looking for damage such as abasic lesions. In humans, the major enzyme responsible for repairing abasic DNA is the endonuclease Ape1. Livermore scientists have been addressing the question of how repair proteins such as Ape1 recognize and bind specifically to damaged DNA.

"We want to know what changes to the DNA shape caused by the lesions are recognized by the repair protein," says Computational Biology Group member Daniel Barsky. Until his simulations were completed last year, scientists had suggested a variety of possibilities.

Using a structurally related protein–DNA complex as a template, Barsky first built a model of DNA bound to Ape1 to guide BBRP biologist David Wilson III and colleagues in determining which amino acids of Ape1 might be most important for its activity. Wilson also synthesized different forms of DNA to see which, if any, would be recognized by Ape1. Surprisingly, all of the altered forms attracted Ape1 to a significant degree. Spurred by Wilson's findings, Barsky used a cluster of advanced scientific workstations in the Livermore Open Computing Facility to complete the first full molecular dynamics simulations of the damaged DNA.



A model of Ape1, a DNA-repair protein, binding to a strand of DNA. DNA strands are in yellow and green, the protein is in blue, and ultraviolet-absorbing amino acids are in red.

The simulations focused on a stretch of DNA with an abasic lesion surrounded by thousands of water molecules. Although the computations simulated a time span of only 2 billionths of a second, they required the equivalent of several months of processing time on a fast single-processor computer.

Shape Changes Flag Enzyme

The results showed that the abasic site does not form a permanent hole or gap in the DNA, as some researchers had postulated. Instead, the missing base causes changes to the internal motions of the DNA—changes that are thought to be important for damage recognition by the repair enzyme.

For example, at various intervals in Barsky's simulations of damaged DNA, a thymine base unpaired with adenine and paired instead with the cytosine base that was opposite the abasic site, where a guanine would normally be. This transient thymine–cytosine base-pair mismatch had not been previously observed. Another clearly visible change was that the sugar molecule, formerly attached to the missing guanine, flipped out of the chain.

The results indicated that the abasic DNA chain has a great deal more flexibility and bending than normal. This unnatural flexibility apparently "flags" the repair protein, says Barsky. Further proof for this concept was supplied last year when x-ray crystallography studies of abasic DNA bound to Ape1 showed a kink in the DNA at the abasic site.

The results from the simulation are being used to determine how specific

differences in the Ape1 protein that have been found in a portion of the human population affect the DNA repair capacity of those individuals. Such knowledge will help researchers predict which people are at greater risk of developing disease from environmental exposures that induce the formation of abasic lesions.

Barsky has also been studying the base pairings in parallel-stranded DNA, a novel form of DNA in which both strands are oriented in the same direction instead of aligning in opposite directions. His quantum chemical calculations contradict previous theories of how the guanine–cytosine base pairing might occur in parallel DNA. The results predict that the greatest stability occurs through an orientational "wobble" in which guanine and cytosine form only two hydrogen bonds instead of the three bonds they form in normal DNA.

Zooming In on Key Ions

Barsky's DNA simulations are magnified a millionfold in simulations done by colleagues Eric Schwegler and Felice Lightstone. Their focus is on the chemical reactions involved in phosphate hydrolysis, an essential part of DNA repair. To study this reaction, they first slice a strand of DNA in two to see how other enzymes repair the damage.

Lightstone's first-principles molecular dynamics simulations use 65 water molecules, one dimethyl phosphate (the simplest repeating structure comprising the DNA backbone), and one magnesium ion in a cubic "box." The model includes a magnesium ion because many DNA-cutting enzymes such as Ape1 require the ion to catalyze the DNA cleavage. In fact, a high concentration of magnesium ions alone can catalyze the cleavage.

The simulations track the movement of every atom and its cloud of electrons. Of particular interest is what happens to the magnesium ion. It attracts six water molecules and momentarily adheres to the dimethyl phosphate, thus making the cleavage reaction possible.

The simulations are run on the ASCI Blue supercomputer using Lawrence Livermore software adapted for multiprocessor machines. Despite the enormous computational power of the computer, Lightstone can only simulate one trillionth of a second per month. "As a result," says Lightstone, "we have to be selective in what we simulate."

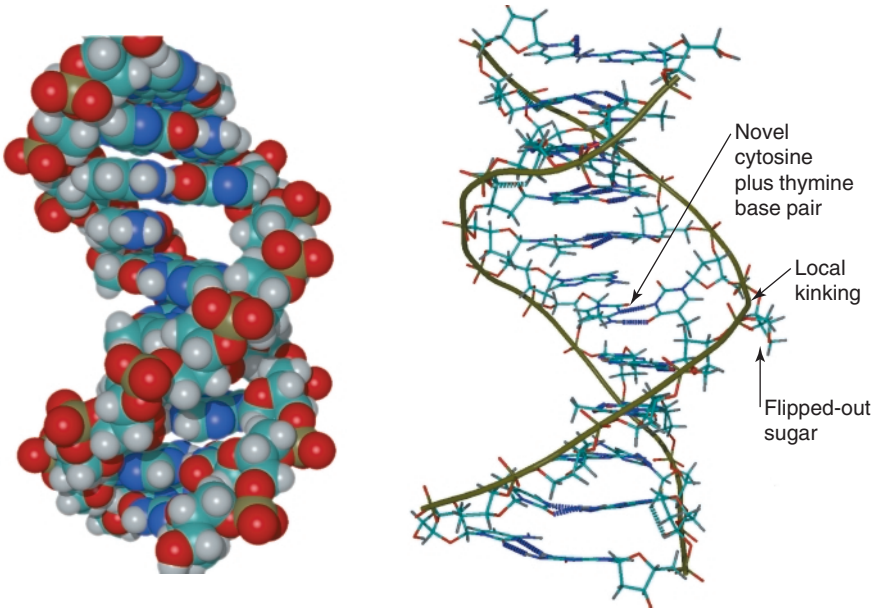
The payoff is new understanding of the pathways of reactions involved in DNA repair. "Experimentalists can't tell you all the steps involved in a biological process," Lightstone says. "Seeing all the steps gives us ideas about how we might modify the reaction or even control the enzyme's actions."

Selective Docking to Enzymes

Lightstone is also working on so-called computational docking to help identify small molecules called ligands. Ligands can uniquely bind to selected sites on proteins, including DNA-repair enzymes and deadly neurotoxins such as tetanus and its relative, botulinum. The identified ligands would be used in sensors to indicate the presence of neurotoxins. The effort is being pursued in conjunction with BBRP researcher Rod Balhorn, Livermore's Chemical and Biological Nonproliferation Program, and computational experts at Sandia National Laboratories. (See *S&TR*, April 1999, pp. 4–9.)

Proof-of-principle computational docking calculations were first used to screen the Available Chemicals Directory—a listing of some 250,000 purchasable compounds for which the three-dimensional structure is known—for chemicals that would bind to the tetanus protein. A cluster of scientific workstations using molecular mechanics techniques required only 10 seconds to analyze the shape of each candidate molecule and determine the extent, if any, to which it could bind to a small depression in the tetanus protein's surface.

After three days of calculations, the simulation had ranked all of the compounds in the chemical library, out



The model at left shows a DNA molecule missing one of its bases. The simulation at right reveals its kinked, unnatural shape that "flags" the repair protein Ape1.

Using a Virtual Microscope

For Lawrence Livermore computational biologist Mike Colvin, the most difficult aspect of designing and running a biological simulation is fully understanding the biological problem at hand and reducing it to one or more key chemical reactions. An example is determining why one molecule is vastly more toxic to a cell than another chemically similar molecule.

"The first step in our job is to dig through the literature and talk with the experimental collaborators to identify the essential reactions that we need to simulate in order to discover the differences in toxicity," says Colvin. Such simulations reveal the exact physical mechanisms and energetics of the process.

Colleague Daniel Barsky calls advanced biochemical simulations a "virtual microscope." This microscope, he explains, combines powerful computers and software programs that link the laws of physics and chemistry to structures of biological molecules that have been determined by x-ray diffraction and other experimental methods.

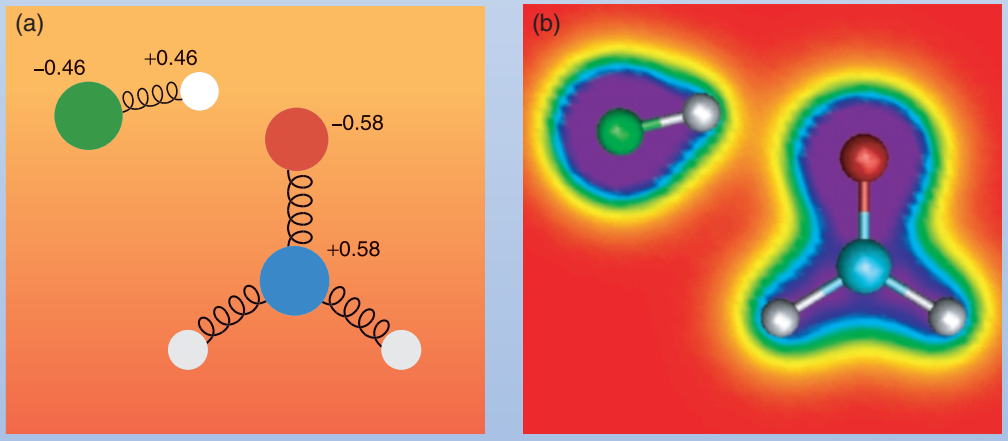
He cautions, however, that one danger with the microscope analogy is that scientists new to such techniques may be tempted to simulate everything without carefully identifying the biological question being addressed. "We have found that the simulations must be very closely tied to experiments. Without having specific things to test and look for, your simulations may produce a mountain of data that do not reveal much."

The biochemical simulations principally take two forms: molecular dynamics and first-principles quantum chemistry. Molecular dynamics is used for DNA and protein studies involving tens of thousands of atoms at a time. These simulations depict atoms like balls interconnected with springs to approximate their motions and their interactions with other atoms.

Simulations based on first-principles quantum chemistry accurately predict the chemical properties of atoms and molecules. The technique uses quantum mechanics to determine the distribution of electrons around each atom. From this electron distribution, any chemical property can be determined, including the structures and energies of molecules.

Teraops-scale supercomputers have made it possible to do so-called first-principles molecular dynamics in which the motion of molecules is simulated using accurate quantum chemical interactions. These methods have been developed by Lawrence Livermore physicists Francois Gygi at the Center for Applied Scientific Computing and Eric Schwegler and Giulia Galli in the Physics and Advanced Technologies Directorate. The new techniques are being applied to selected biochemical problems, such as how DNA is cleaved by repair enzymes and how an anticancer drug is activated by the body.

Frequently, different simulation methods are used together to solve a single problem. For example, a researcher can do molecular dynamics on DNA structure, then pull out a small area of interest and do first-principles simulations for understanding the exact electronic forces at play.



Examples of two modeling methods applied to the interaction of hydrogen fluoride and formaldehyde. (a) Molecular dynamics models depict atoms like balls interconnected with springs to simulate their motions. (b) First-principles simulations use quantum mechanics to predict the chemical properties of atoms and molecules.

of which Lightstone compiled a list of 11 candidates for laboratory tests. BBRP experimentalists found that 5 of the 11 molecules successfully bound to the tetanus protein.

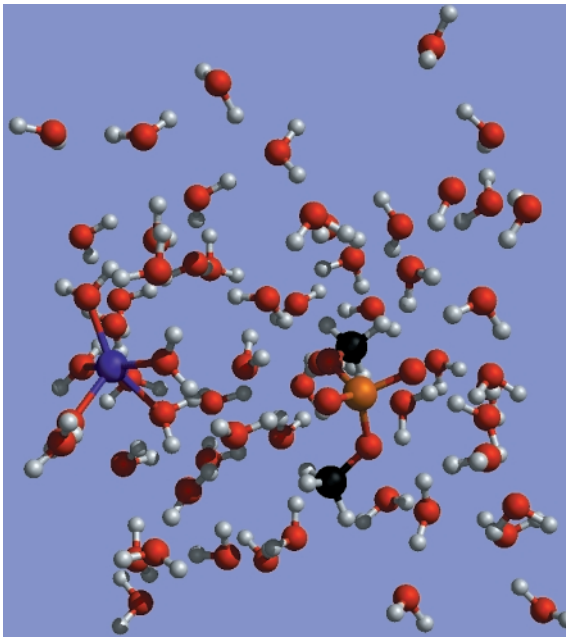
Lightstone points to the efficiency of using methods such as computational docking as a screening tool. "Experimentally testing 250,000 compounds would take years of work," she says. She notes that the docking simulations are done at a coarse level of accuracy. "If you did them at first-principles level, we would get bogged down in long computer times. Our purpose is to screen lots of compounds very quickly."

Lightstone moved on to finding candidate ligands for binding to botulinum toxin, which is viewed as a more dangerous threat. This time, she applied a second computational step, flexible docking, to the top 2,000 compounds identified in the first step. Flexible docking, which requires two additional weeks of computer time, rotates molecular bonds to find the optimum shape of a molecule for binding to a selected protein. The top-scoring ligands are being tested for their affinity to the botulinum protein.

To increase the sensitivity and selectivity of a portable sensor, Lightstone is searching for an additional ligand for a second, nearby site on the botulinum protein. Together, the two ligands could be used to detect the toxin at low concentrations.

Mutagens Get Activated

The longest running collaborative project in the Computational Biology Group is studying the function of mutagenic chemicals called heterocyclic amines. These compounds are formed in the cooking of several foods and may be a risk factor associated with cancer in the human digestive tract. As with most substances that damage DNA and cause cancer, the food mutagens must be activated by metabolic reactions the body uses to break down chemicals. Once activated, the mutagens bind to DNA and can interfere with the accurate duplication of the genetic code, thereby leading to mutations and eventually cancer.



This simulation focuses on magnesium, which is required by many DNA repair enzymes. The simulation includes many water molecules and one dimethyl phosphate molecule (the simplest repeating component of DNA). Oxygen is red, hydrogen is white, carbon is black, magnesium is purple, and phosphate is orange.

For the past four years, the group has been applying simulations to help experimentalists identify a subset of heterocyclic amines called 2-aminoimidazole-azarene (AIA) compounds. The group is looking at several properties of these mutagens, including the metabolic steps that actuate the compounds, the initial attachment site of these mutagenic compounds on DNA, how binding to the mutagens depends on the DNA sequence of bases, and the effect of different cooking processes on mutagen formation.

"A paradox is that all two dozen molecules in the AIA family are chemically similar, and yet there is a 10-millionfold range in mutagenicity," says Colvin. Identifying the factors that vary the potency will help scientists better predict the human health risks associated with exposure to food mutagens.

The most recent simulations involve the action of cytochrome P450, the enzyme responsible for first activating the mutagens. Because the structure of the human form of P450 is unknown, the group built a computer model using related enzymes whose structure is known. The simulations are used to dock different AIA compounds into the enzyme's active site to determine if the more potent species make a better fit and are thus more likely to become activated.

The group is also simulating the interaction between P450 and members of the bioflavanoid family, which inhibit food mutagens. About the same size and shape as AIA compounds, bioflavanoids are found in fruits and vegetables. One hypothesis is that the bioflavanoids lower the incidence of food mutagens by competing for the same activation site on P450 as the AIA compounds.

A Virtual Frypan

A new effort in the Computational Biology Group is to develop an accurate computer model of cooking hamburger patties and other meats. The goal, says student researcher Ngoc Tran, is to successfully simulate what BBRP investigators do on a hot stove to study how cooking methods affect food mutagen production. Thus, virtual cooking would help reduce the number of experiments done in the kitchen by identifying the key experimental measurements that must be made.

Developing a simulation of the cooking process and the formation of mutagens is not straightforward because it must reflect such factors as the fat and moisture content of the meat, the frying temperature, the heat conductivity of the pan and the meat, and the manner of cooking. For example, BBRP researchers discovered last year that flipping a hamburger frequently during frying reduces the number of mutagens. (See *S&TR*, January/February 2001, p. 2.)

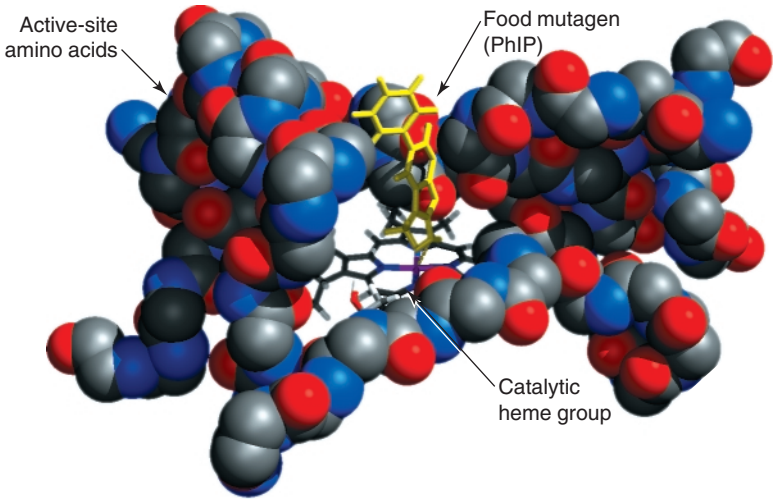
Tran spent last summer working with Mark Knize and Cyndy Salmon accumulating raw data for the simulations by cooking a couple dozen hamburgers. She measured the temperature at different depths of the patties as well as the corresponding concentrations of AIA compounds. She found that the first millimeter contained 50 percent of the food mutagens, the second millimeter contained 25 percent, and the third contained 10 to 15 percent. The simulations accurately reproduced the temperature profiles measured while cooking beef patties and correctly predicted how the concentration of mutagens varied at different meat depths.

The current goal is to refine the model so that it accurately reflects every aspect of cooking. Simulations will then be used to determine the sensitivity of mutagen formation to such parameters as fat content and pan temperature. The ultimate goal is to design new cooking procedures that minimize the formation of mutagens.

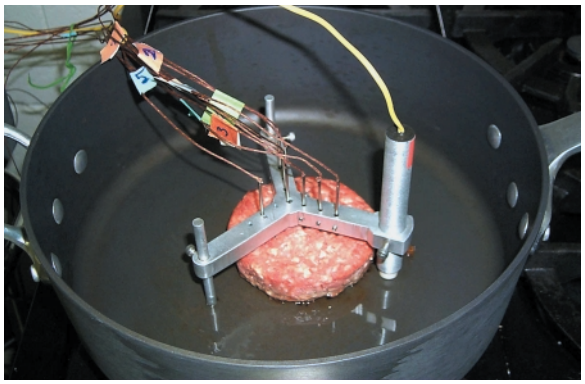
Optimizing Anticancer Drugs

Simulations are also helping scientists to understand the functioning of one of the oldest families of anticancer drugs, the phosphoramidic mustards. The group includes the widely used drugs cyclophosphamide and ifosfamide. These drugs are closely related to the poisonous mustard gas used in World War I. Doctors noticed at the time that the gas killed rapidly dividing body cells and reasoned that a derivative might work on cancer cells because they continually divide.

Despite being used for more than 40 years, several important questions about the drugs' biological activity remain unanswered. The key to the drugs' therapeutic activity—and toxic side effects—are the activation steps they undergo in the body before they bind to DNA.



This simulation reveals the binding mechanism between a food mutagen and cytochrome P450, the enzyme that catalyzes the initial activation step for this mutagen.



A fully instrumented hamburger patty is fried to determine its temperature as a function of depth as well as the corresponding concentrations of food mutagens. The data are used to develop computer simulations of the cooking process and to predict the formation of mutagens.

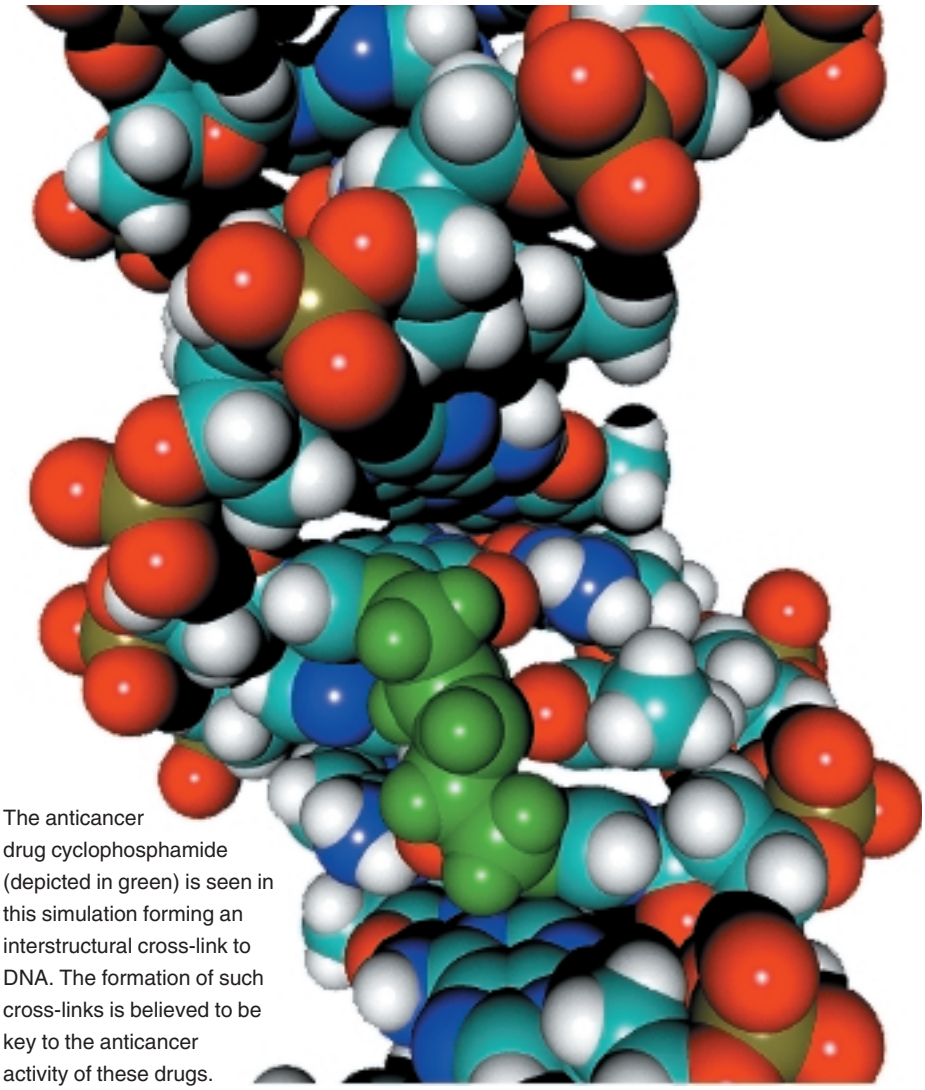
Colvin has been collaborating with scientists at Duke University's Comprehensive Cancer Center to understand how the activation reactions affect the drugs' potency. Fortunately, the drugs are small enough to be modeled using first-principles methods. Simulations of most of the steps in the activation pathway have helped to explain several unexpected properties of these drugs and are suggesting improved versions of the standard mustard drugs.

Mustard drugs are known to kill cancer cells by forming cross-links between the two strands of a cell's DNA. These cross-links are particularly difficult for a cell to eliminate; just a few cross-links kill a cancer cell. Colvin and Dat Nguyen, a graduate student researcher from the University of California at Davis, are simulating how cyclophosphamide forms cross-links. The goal is to understand how the drug's molecular structure could be changed to make it more effective in forming cross-links.

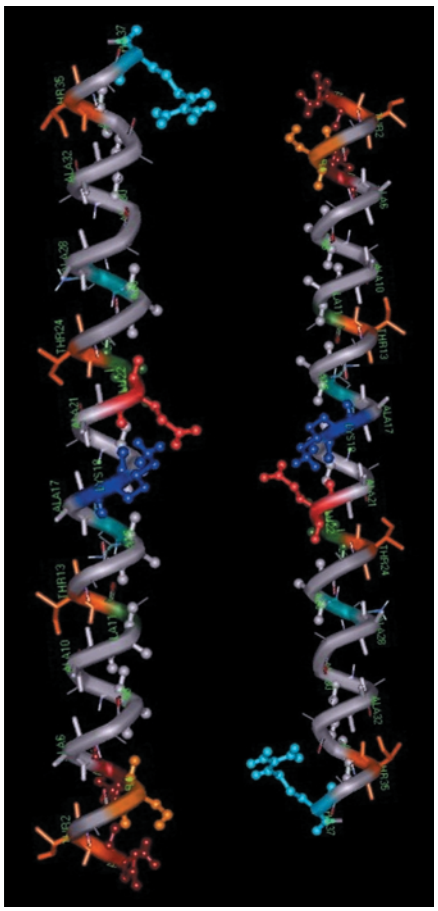
Researchers at Duke University and the University of Chicago will synthesize the best molecular candidates identified in the simulations and test their cross-linking capacity on DNA. The most promising molecules will then be tested for their effectiveness in killing cancer cells.

Antifreeze Needed Here

The Computational Biology Group is also collaborating with Nguyen and several UC Davis professors to



The anticancer drug cyclophosphamide (depicted in green) is seen in this simulation forming an interstructural cross-link to DNA. The formation of such cross-links is believed to be key to the anticancer activity of these drugs.



Molecular dynamics simulations indicate how antifreeze proteins in the winter flounder may prevent ice formation by forming several stable structures, like this one, that act as an insulating blanket.

examine a phenomenon that has puzzled biologists for more than four decades: the ability of Antarctic fish to survive sea temperatures well below freezing. The fish contain a variety of so-called antifreeze proteins in their bloodstream that inhibit the growth of ice crystals in their bodies. Similar proteins have also been identified in some insects and plants that can withstand freezing temperatures.

The exact mechanisms of how they function have been a mystery, but molecular dynamics simulations by Nguyen provide new clues. The simulations tested the hypothesis that these proteins depress the freezing temperature by binding to ice crystals and acting like an insulating blanket. The results showed that pairs of antifreeze proteins can form several stable structures. The proteins may be able to absorb and store heat by undergoing transitions between these structures.

Simulations' Value Recognized

Colvin says that Lawrence Livermore's new capabilities in computational biology are being recognized by the greater scientific research community in the form of invited talks, requests for review articles and textbook chapters, and new collaborations by colleagues at universities and companies.

"As computational modeling is successfully applied to more biological problems," Colvin says, "it is clear that simulation will have a growing role in the training and research of biological scientists." There is also little doubt that advanced simulations will continue to change the nature of biological research.

—Arnie Heller

Key Words: abasic lesions, Accelerated Strategic Computing Initiative (ASCI), Ape1, bioflavanoids, botulinum, Center for Applied Scientific Computing, computational biochemistry, cyclophosphamide, DNA, first-principles molecular dynamics, food mutagens, molecular dynamics, quantum mechanics, tetanus.

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About the Scientist

MIKE COLVIN is leader of the Computational Biology Group in Livermore's Biology and Biotechnology Research Program (BBRP). He received B.S. degrees in chemistry and humanities from the Massachusetts Institute of Technology and a Ph.D. in chemistry from the University of California at Berkeley. He joined the Laboratory in 1986 as a postdoctoral fellow in the Institute of Scientific Computing Research and then became a staff physicist in O Division, where he concentrated on designing biologically inspired algorithms for faint object detection. In 1990, Colvin transferred to the Center for Computational Engineering at Sandia National Laboratories, California, to develop quantum chemical methods for massively parallel computers. In 1997, he returned to Livermore and joined BBRP. His research there has focused on using advanced computer simulations to study biological phenomena.

The World's Most Accurate Lathe

THE wood lathe in a home workshop is remarkably similar to Livermore's Large Optics Diamond Turning Machine. Both spin a workpiece while a cutting tool cuts the revolving surface. But their end products bear little resemblance. Built to form large, irregularly shaped mirrors for experimental lasers, the LODTM (pronounced "load 'em") leaves behind a gleaming reflective surface that often needs no further finishing. It is the most accurate large machine tool in the world.

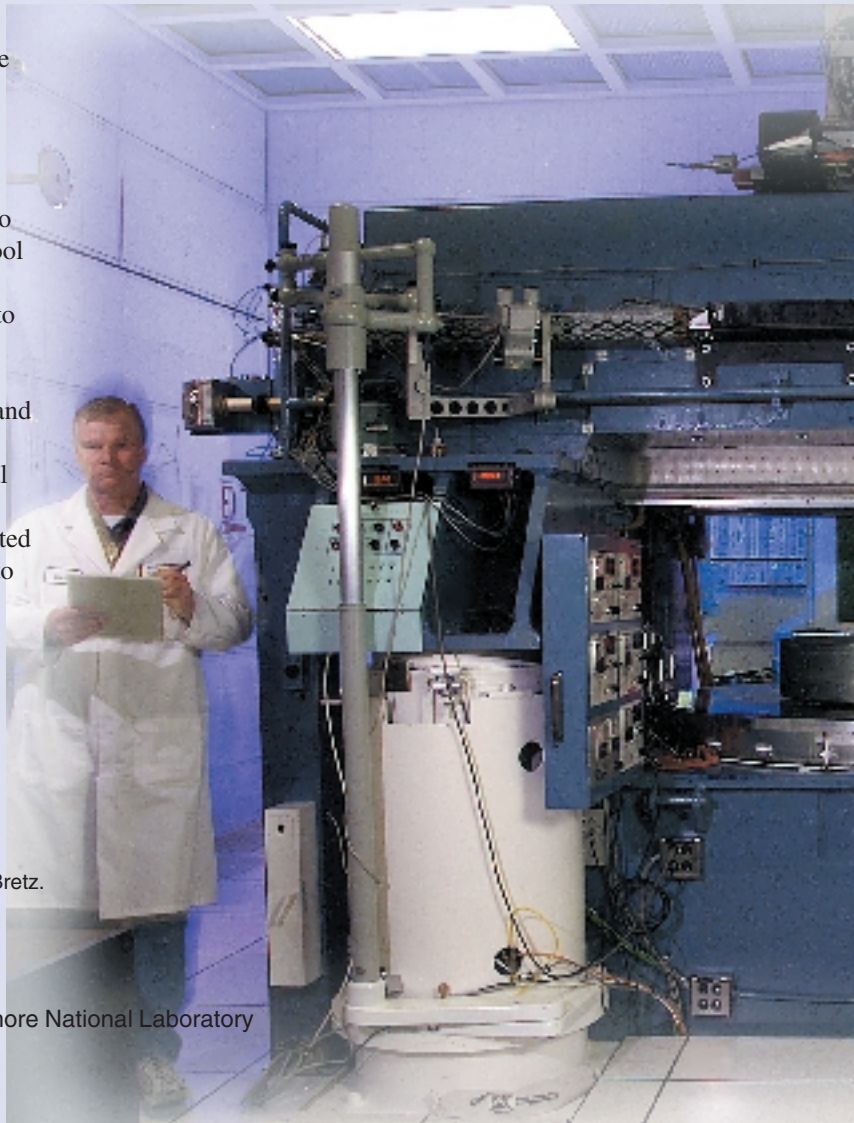
Diamond turning is routinely used today to manufacture contact lenses and parts for videocassette recorders. Defense contractors also use diamond turning to make lenses for heat-seeking missiles and other weapons. All of these products are transmissive optics, meaning that light passes through them. They are also relatively small with a regular, curved shape. Says engineer Jeff Klingmann, leader of the Precision Systems and Manufacturing Group, "That type of diamond turning is a whole different animal from the large, reflective optics we do. Reflective optics—mirrors—are often ground and polished. But that doesn't work for mirrors with aspheric shapes. When the Department of Defense needed large, aspherical metal mirrors back in the early 1980s, Livermore built LODTM. Producing aspherical shapes is no problem. We just program the shape in, and the diamond tool goes to work."

LODTM can handle a workpiece with a diameter of up to 1.65 meters, a height up to 0.5 meters, and a weight of as much as 1,360 kilograms. A diamond the size and quality of a half-carat engagement ring is secured to a steel shank and carried on the end of a vertically moving tool bar. The workpiece rotates about 50 times a minute on the horizontal face plate while the diamond tool cuts gossamer threads of aluminum, copper, silicon, gold, or nickel with unprecedented precision. The LODTM can produce parts with tolerances to 28 nanometers (about a millionth of an inch), accuracy more than 1,000 times greater than that of a conventional machine tool.

Birth of an Ultraprecision Machine

In the 1970s, researchers were considering the development of powerful experimental lasers as an element of missile defense. These ideas became part of the Strategic Defense Initiative, or Star Wars, a program born in the 1980s during the Reagan administration. The laser system's optics had to be extremely large, exotically shaped, and fabricated with a precision corresponding to a small fraction of the wavelength of light. In meeting those requirements, LODTM achieved levels of accuracy that defied measurement by existing methods. Even today, the machine's accuracy is such that it cannot be corroborated by the National Institute of Standards and Technology.

Livermore's Precision Engineering Program designed the machine as the culmination of research in machine tool



The Large Optics Diamond Turning Machine with machinist Steve Bretz.

accuracy. They had determined in the late 1970s that by pushing the limits of precision, they could develop a diamond-turning machine for machining large, oddly shaped optics to exacting tolerances. LODTM incorporated the results of an exhaustive analysis and elimination of factors that cause machine errors, from the heat of a human body to the vibration from a heavy truck passing by.

For example, LODTM has several ways to handle the temperature fluctuations that are typically the largest single cause of diamond-turning machining error. Air temperature in the LODTM enclosure is maintained at precisely 20°C. After the tool is set up, machining does not begin for at least 12 hours to allow the effect of the machinist's body heat to dissipate. All personnel remain outside the LODTM enclosure while a part is being cut. What little heat the diamond cutting tool generates is carried away by cutting oil, also maintained at 20°C.

Engineer Jim Hamilton, who translates client needs into specific instructions for LODTM's machinists, says, "We were concerned that construction for the National Ignition Facility over the last several years might cause us problems. Our building is only about 100 meters away from the NIF construction site. But the earth moving and other heavy work didn't affect the machine."

The heart of the machine's accuracy is a metrology (measurement) frame isolated from the environment by temperature-controlled water flowing through expanded stainless-steel panels. The frame is made of super invar, a steel–nickel–cobalt alloy with one of the lowest coefficients of thermal expansion of any metal. The frame "floats" on LODTM, moving independently from the main machine to give an unstressed, undeformed reference. The part being machined is thus made relative to this frame, not the main machine components. Seven interferometers on the metrology frame continuously measure the location of the tool relative to the part. The machine controller uses this information in real time to dictate all machining. This continuous measurement from an unchanging platform eliminates errors from machine geometry and temperature changes so they do not appear in the part.

LODTM in Action

LODTM continues to produce one-of-a-kind, prototype optical devices for possible future space-based defense systems. The ultimate client is the U.S. Air Force, with Livermore's technical requirements coming from TRW Inc. These conical mirrors are made of silicon for a simple, light, uncooled laser system.

Previously, Livermore used LODTM to produce three secondary mirrors for the Keck telescopes on Mauna Kea on the Big Island of Hawaii. The Keck telescopes, the largest and most powerful in the world, gather infrared light rather than visible light. For infrared astronomy, diamond turning was the

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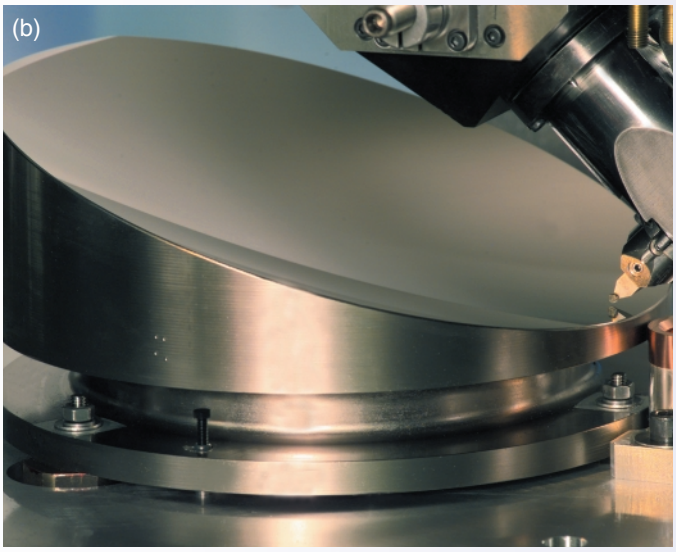
An example of the aspherical mirrors that the Large Optics Diamond Turning Machine first produced.



(a) National Aeronautical and Space Administration engineer Holly Cagle examines SPARCLE's primary mirrors on the Large Optics Diamond Turning Machine (LODTM) spindle. (b) A close up of a mirror and the diamond tool on LODTM.

only viable process because the mirrors had to be accurate right to the edge of the reflective surface. Processes such as grinding and polishing round off or taper the edge of the critical surface.

Livermore used two precision machining tools, the Diamond Turning Machine #3 and LODTM, to produce the primary mirrors for SPARCLE, an experiment on National Aeronautical and Space Administration's (NASA) Space Shuttle. SPARCLE will demonstrate the ability to measure wind speeds using a space-based lidar system. Diamond Turning Machine #3 first semifinished an aluminum blank that was then coated with electroless nickel. LODTM did final "figuring" in the nickel layer. After leaving Livermore, the mirrors were polished and gold coated for final use.

LODTM Today

The next big project for LODTM may be for NASA scientists who are planning a new space-based telescope. LODTM has the capability to machine some or the mirrors for this next-generation version of the Hubble telescope.

A staff of seven operates and maintains LODTM, about half the number required when the machine first came on line. Over the years, many original, custom-made parts have been replaced by commercial ones. The result is a more efficient and reliable machine that is easier to operate and maintain.

But LODTM is nevertheless a unique machine, and it must machine parts to extremely tight tolerances. Says Steve Bretz, head machinist on LODTM, "We spend about 80 percent of our time keeping the machine running properly. Before I came to Livermore, I was a machinist in a regular machine shop. Working on LODTM is entirely different. Here we have to work very closely with engineers and experts in computers, electronics, and control systems to eliminate deviations and maintain the required tolerances."

They must be doing something right. Eighteen years after LODTM's first operations, measuring devices are still not sophisticated enough to confirm the machine's accuracy.

—Katie Walter

Key Words: Keck telescopes, Large Optics Diamond Turning Machine (LODTM), National Aeronautical and Space Administration (NASA), precision engineering, Strategic Defense Initiative.

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Leading the Attack on Cancer

LAST October, Lawrence Livermore joined forces with the University of California at Davis Cancer Center to fight cancer, the nation's second leading killer. Together, they are researching cancer biology, prevention, and control as well as new cancer detection and treatment techniques.

During a ceremony to announce the collaboration, Livermore Deputy Director for Science and Technology Jeff Wadsworth noted that the collaboration reflects the principles on which Ernest Lawrence founded the Laboratory. "One of those principles was that the Laboratory should work on problems of national importance using multidisciplinary teams on projects of scale," he said. "I think this collaboration exemplifies those principles. Solutions to cancer are of great national importance, and we're using multidisciplinary teams from this Laboratory and UC Davis in this effort."

Livermore brings to the venture its multidisciplinary staff of scientists and engineers, supercomputing expertise, and a biomedical research program that dates back to the early 1960s. The UC Davis Cancer Center contributes its patient-centered research and clinical experience. The collaboration offers a clinical testing ground for medical technologies that Livermore develops.

Over the years, Livermore has developed expertise in DNA repair, cancer susceptibility, dietetic carcinogenesis, genetic toxicology, structural biology, genomics, and biotechnology. Livermore in collaboration with Lawrence Berkeley and Los Alamos national laboratories formed the Joint Genome Institute to decode three chromosomes for the Human Genome Project. Livermore is also one of the few research institutions in the world that is applying accelerator mass spectrometry to biological research (see *S&TR*, November 1997, pp. 4–11, and July/August 2000, pp. 12–19). With this ultrasensitive measuring technique, most commonly used to trace carbon-14 in samples for carbon dating, scientists can for the first time measure how typical doses of a suspected carcinogen affect DNA. Scientists from Livermore and UC Davis are already using it to learn more about how we metabolize vitamins and other nutrients.

Scientists from UC Davis and Livermore have been performing research together for several years. A few Livermore scientists are already adjunct professors at UC Davis. This collaboration brings the two organizations together on a more formal basis, making it easier for these two parts of the University of California to work together in the future. Under the terms of the agreement, molecular biologist Jim Felton, a Livermore specialist in cancer causation and prevention, and physicist Dennis Matthews, leader of Livermore's Medical Technology Program, have been named associate directors of the UC Davis Cancer Center. Felton is also the Livermore liaison to UC Davis for all work associated with the collaboration.

Much Work in Progress

Together, Lawrence Livermore and the UC Davis Cancer Center have about 200 scientists and physicians working on cancer research projects. Their work falls into six areas: molecular oncology; cancer biology in animals; cancer therapeutics; cancer etiology (causation), prevention, and control; prostate cancer; and biomedical technologies. Each research area has 25 or more researchers involved, with participants from both Livermore and UC Davis.

Livermore researchers are participating in all six research areas and are taking a leadership role in three of them. Felton

Lawrence Livermore National Laboratory

is co-leader of research on cancer causation, prevention, and control. Matthews is co-leading the work on biomedical technology. Toxicologist Ken Turtletaub is co-leader of molecular oncology research.

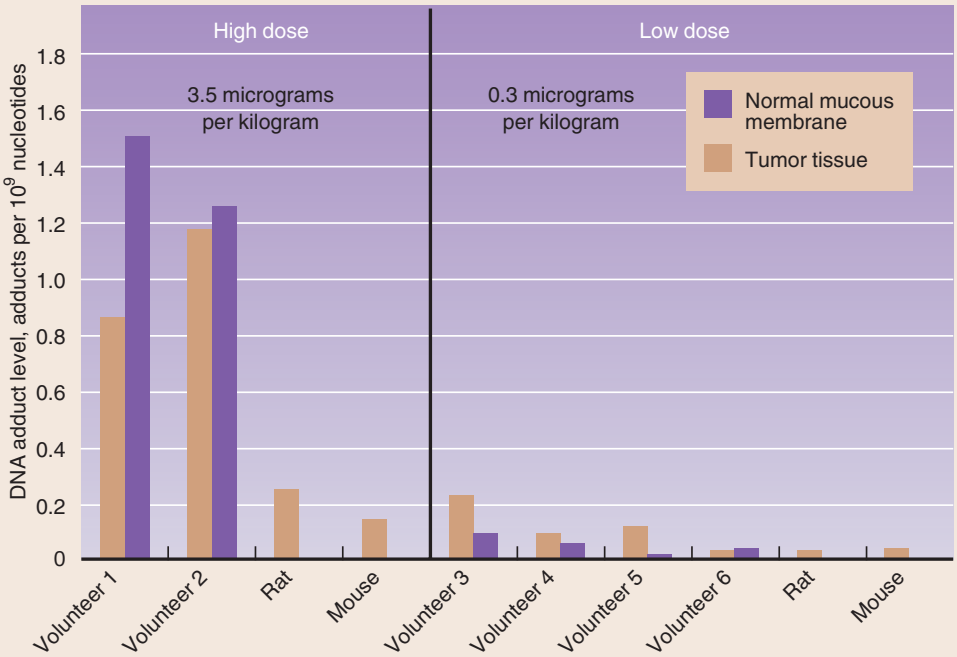
The team headed by Felton and Marc Schenker, M.D., of UC Davis seeks to better understand the causes of cancer and then to develop and implement strategies to reduce cancer incidence and morbidity. Their work focuses on three causes of cancer—tobacco, nutrition, and environmental exposures. For many years, Felton has been studying the effects of diet on carcinogenesis, in particular, how heterocyclic amines produced during the cooking of meats may damage DNA and ultimately cause cancer. Other joint dietary studies are examining the role of selenium and folate in preventing cancer. Says Felton, "We are also tackling the effects of tobacco smoke constituents on rodent and human lung cells and tissue. Working with the California State Department of Public Health, we are studying methods to convince people to stop smoking."

Under Matthews and UC Davis Professor of Radiology John Boone, the biomedical technology program combines expertise in physical and life sciences and engineering to create new devices and technologies. The emphasis is on imaging and diagnostics research and the development of therapeutic devices. About 20 projects are under way in these areas. For example, using ultrashort-pulse technology developed at Livermore, a joint team is developing a diagnostic tool that creates images showing melanomas and other cancers on the surface of the skin. One therapeutic device is PEREGRINE, a new approach developed at Livermore to planning radiation therapy for treating cancer (*S&TR*, May 1997, pp. 4–11, and October 1999, pp.14–15). PEREGRINE was recently cleared by the U.S. Food and Drug Administration for use in clinics and hospitals. The project team has turned its attention to developing imaging simulation codes as well as the means to plan radiation therapy using internal radiation sources.

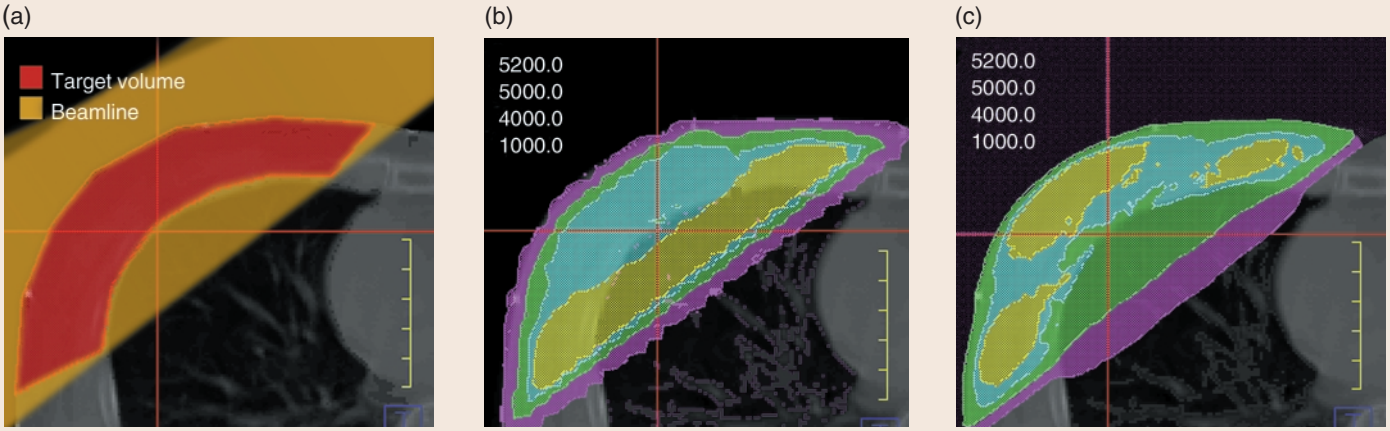
Turtletaub and molecular biologist Hsing-Jien Kung of UC Davis are managing research on molecular oncology. They are examining the fundamental processes of cancer biology from the initial "insult" to the cell through the intermediate and later responses of the cell, be they negative effects of the carcinogen or the healing effects of therapy. Turtletaub is overseeing the work related to DNA damage and cycle checkpoints, continuing a long-term study of DNA damage and repair. The team hopes to quickly translate its discoveries about cancer mechanisms into the development of prognostic markers and curative therapies.

A New Approach to Commercialization

Livermore is taking a new approach to getting its technologies commercialized and available for use by physicians and patients. Along the lines of the joint cancer center, Livermore and UC Davis have initiated a joint Bio



In earlier work, Livermore researchers found that rodents and humans exhibit significantly different responses to high and low doses of MelQx, a chemical that appears in meat after it is cooked. MelQx causes damage to DNA. Scientists from Livermore and the University of California at Davis will continue this work and perform similar experiments to determine the effects of tobacco on humans and rodents.



This breast cancer case highlights the importance of accurate dose calculations for correct dose coverage of a tumor and sensitive surrounding lung tissue. (a) The radiation applied to the target is shown in general. (b) While conventional dose calculations show that the prescribed dose level covers the entire tumor, (c) PEREGRINE calculations suggest that for this treatment, the prescribed dose shows a higher skin dose, deeper penetration of dose into the lung, and a different dose distribution within the chest wall.

and Medical Technology Development Industrial Partners Consortium. By working together, Livermore, the UC Davis Health System, and industrial partners form a complete "laboratory bench-to-bedside" cycle for innovative medical technologies. Livermore's Medical Technology Program and Biology and Biotechnology Research Program and the UC Davis Health System are experienced in identifying critical medical needs, researching new concepts, and developing prototype devices. The industrial partners will develop these devices into commercial products, shepherd them through the approval process, and distribute them to the medical profession.

Formed at about the same time as the joint cancer center, the Industrial Partners Consortium is not limited to technologies related to cancer. More than 50 participants from 30 companies attended the first presentation by the consortium in November 2000. Since then, numerous companies have expressed interest in working with Livermore and UC Davis, and one partnership has officially been formed.

Toward Becoming an NIH Cancer Center

Another major goal for the Livermore and UC Davis collaboration is to become a designated cancer center by the National Cancer Institute (NCI). One of the National Institutes of Health, NCI funds 60 cancer centers throughout the U.S. These centers emphasize multidisciplinary cancer research as well as public information, education, and outreach. NCI's decision on the collaboration's application to become a designated cancer center is expected in the fall of 2001.

NIH funding would not be for specific projects but for overhead support and would thus free many scientist–administrators to perform more actual research. The funding would also help initiate collaborations between institutions and provide seed money for new areas of research that support the six themes of the cancer center.

Cancer has or will touch the lives of almost everyone in the country at some time. Yet only about half of all newly diagnosed cancer patients can be treated effectively with available therapies. Increasing that percentage—and finding better ways to prevent, detect, and diagnose the disease—will benefit us all.

—Katie Walter

Key Words: cancer research, National Cancer Institute (NCI), PEREGRINE, University of California at Davis.

For further information contact Jim Felton (925) 422-5656 (felton1@llnl.gov), Dennis Matthews (925) 422-5360 (matthews1@llnl.gov), or Ken Turtletaub (925) 423-8152 (turtletaub2@llnl.gov).

Electronic Memory Goes High Rise

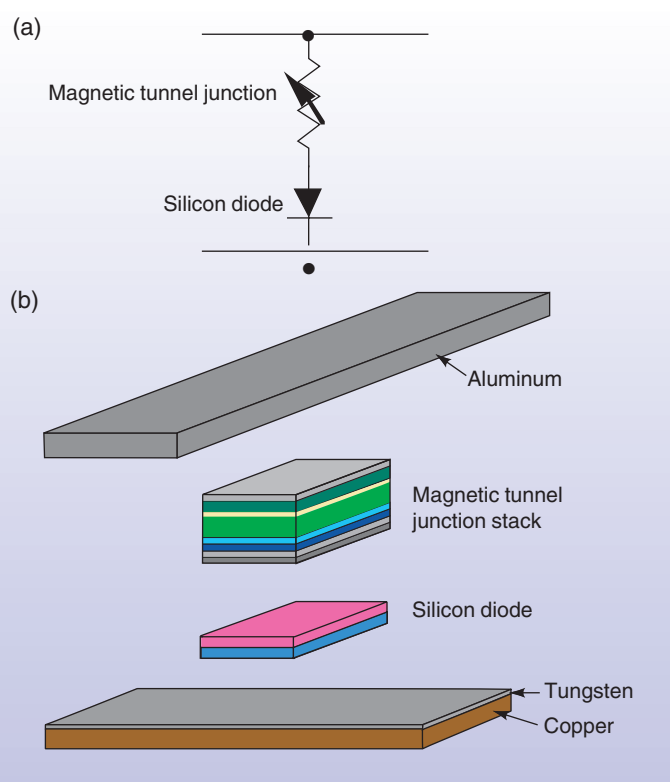
THE processing speed of the average commercial desktop computer is increasing at a good clip. At the same time, memory latency—or the time it takes for a computer's central processing unit to grab a piece of information stored in random access memory (RAM)—is increasing much less quickly. One problem is that in conventional dynamic random access memory (DRAM) or static random access memory (SRAM), each line in a two-dimensional memory array is managed by one switch. The farther a piece of memory is from the switch or central processing unit, the longer it takes to retrieve it. This problem is compounded by the complicated code and data structures in modern software applications that require access to a vast amount of random memory.

Reducing memory latency is one of several major challenges to developing the massively parallel computers of the Accelerated Strategic Computing Initiative (ASCI) beyond the next generation. ASCI computers are a key component of the Department of Energy's program for stewardship of our nation's stockpile of nuclear weapons. Combined with nonnuclear experiments, simulations of nuclear implosions and other phenomena in three dimensions are needed so that scientists can assure that the stockpile remains safe and secure without underground nuclear testing. The current ASCI White computer, the most powerful in the world, operates at 12 teraops (trillion operations per second). The next-generation ASCI computers will operate in the 30 to 70 teraops range. However, the imbalance between microprocessor speed and the delivery time of information to the processor will hamper further ASCI development and severely limit performance.

Scientists at Livermore think that magnetic random access memory (MRAM) might be one solution to the memory latency problem. They are working on integrating a diode switch on top of the magnetic tunneling junctions that make MRAM work, creating more efficient vertical RAM. Mathematical physicist Charles Cerjan, who is leading work on MRAM at Livermore, says, "To decrease memory latency, we want to get away from the flat suburban sprawl of today's memory systems and create high-density 'skyscrapers' of RAM."

In addition to speeding up information access, MRAM offers several other advantages. It is immune to radiation damage, consumes little power, and continues to function over wide temperature ranges. Unlike most other forms of RAM, magnetic RAM is nonvolatile, which is to say that it retains its memory even after power is removed. For example, after the explosion of the space shuttle Challenger in 1986, NASA was able to retrieve the shuttle's magnetic memory—still readable—from the bottom of the Atlantic Ocean.

Magnetic memory has been around for a long time as cassette tapes and disk drives. But until recently, fast, high-density MRAM was not possible because the access times to read and write data were inferior to those in semiconductor-based memory. Great strides have been made in manufacturing thin-film multilayers, which are key to MRAM's operation. Challenges remain, however. Primary among them are finding the right combination of multilayers



(a) A simplified circuit diagram showing the configuration of a magnetic memory cell containing a magnetic tunnel junction. (b) An expanded view of the multilayer stack and diode configuration.

to maximize their performance and attaching a microprocessor to the magnetic material to bring memory and processing as close together as possible.

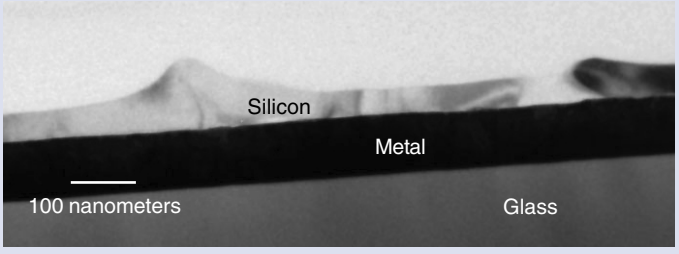
Building on Success

Livermore's current work on MRAM is the successor to a magnetic ultrahigh-density read head for computer disk drives, for which Cerjan and other Livermore researchers won an R&D 100 Award in 1996 (see *S&TR*, October 1996, pp. 24–25). Using Livermore's expertise in thin, multilayer films and microfabrication technologies, they developed a layered sensor that is smaller and offers better performance than conventional magnetic sensors. It has alternating magnetic and nonmagnetic layers, each less than 5 nanometers thick. The total thickness of the sensor is only about 100 nanometers, or about one-thousandth the width of a human hair.

Working with two industrial partners to commercialize the device, the Livermore researchers modified their original design into a magnetic tunnel junction, in which an insulating barrier is inserted between two different types of magnetic material. When a current is applied perpendicularly to the layers, it "tunnels" through the insulator. The relative magnetic field alignment of the two separated magnetic materials induces either a low- or high-resistance current path. This resistance difference can be identified as a stored bit of information, either a 0 or a 1. Already, these individual memory elements have comparable or superior performance to any reported in the literature.

Overcoming Incompatibilities

Experiments are under way to attach a diode switch to this magnetic sandwich, the first step before attempting to attach a microprocessor. Standard mechanisms for processing semiconductor and magnetic materials are normally incompatible. Semiconductor materials require high temperatures to fabricate parts, but magnetic materials lose their magnetic properties if heated above approximately 300°C. The team is experimenting with low-temperature laser annealing, a technique developed at Livermore. Because the thermal penetration depth of the laser annealing process is relatively shallow, a diode switch can apparently be fabricated on a multilayer stack of magnetic materials without adversely affecting the storage characteristics of the adjacent memory device. Says Cerjan, "We have been able to heat just one layer of the amorphous silicon so that the metal beneath it is not damaged."



A cross section of polycrystalline silicon grown on a metal substrate by laser annealing, as seen through a transmission electron microscope.

Within the next year, the team plans to integrate the diode switches and relatively large MRAM cells on 4 by 4 arrays of 10-micrometer cells. If they are successful in installing a diode switch in the magnetic tunnel junction cells, they will have produced individually addressable random access memory elements. The next step will be to make these devices even smaller to achieve higher density and hence improved performance. Further development will require the participation of a commercial partner to ensure that the design is practical and that the devices can be readily manufactured.

Spin-Offs from Spin Electronics

Aligning the magnetization of the two layers in magnetic tunnel junction alters the spin polarization of the conducting electrons. The alterations in spin polarization, in turn, affect the overall tunneling probability and hence the magnetoresistive ratio (that is, the ratio of change in electrical resistance when a magnetic field is applied). To date, the team has measured resistance ratios as high as 25 percent, which is large enough to make MRAM elements competitive with semiconductor-based memory.

These developments have prompted Livermore researchers to investigate new classes of so-called spintronic materials, which put both the charge and spin of the conductive electrons to work. A potential application of these new materials would be in secure quantum communication and perhaps, in the future, in quantum computers. Quantum communication is inherently "unbreakable"—any attempt to intercept it destroys the signal. Quantum computers are considerably farther down the road. Replacing the linear computers of today, quantum computers would entangle all functions and solve them at once. Such computers sound like science fiction today but may be reality some day.

—Katie Walter

Key Words: magnetic random access memory (MRAM), magnetic tunnel junctions, Accelerated Strategic Computing Initiative (ASCI).

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Patents and Awards

Each month in this space we report on the patents issued to and/or the awards received by Laboratory employees. Our goal is to showcase the distinguished scientific and technical achievements of our employees as well as to indicate the scale and scope of the work done at the Laboratory.

Patents

Micromachined Magnetohydrodynamic Actuators and Sensors

Abraham P. Lee, Asuncion V. Lemoff
U.S. Patent 6,146,103
November 14, 2000

A magnetohydrodynamic (MHD) micropump and microsensor that uses micromachining to integrate the electrodes with microchannels and includes a magnet for producing magnetic fields perpendicular to both the electrical current direction and the fluid flow direction. The magnet can also be micromachined and integrated with the micropump using existing technology. The MHD micropump, for example, can generate continuous, reversible flow, with readily controllable flow rates. The flow can be reversed by either reversing the electrical current flow or reversing the magnetic field. By mismatching the electrodes, a swirling vortex flow can be generated for potential mixing applications. No moving parts are necessary, and the dead volume is minimal. The micropumps can be placed at any position in fluidic circuit, and a combination of micropumps can generate fluidic plugs and valves.

Using Electrical Impedance Tomography to Map Subsurface Hydraulic Conductivity

James G. Berryman, William D. Daily, Abelardo L. Ramirez, Jeffery J. Roberts
U.S. Patent 6,147,497
November 14, 2000

Electrical impedance tomography (EIT) can be used to map hydraulic conductivity in the subsurface where measurements of both amplitude and phase are made. Hydraulic conductivity depends on at least two parameters: porosity and a length-scale parameter. Electrical resistance tomography (ERT) measures and maps electrical conductivity (which can be related to porosity) in three dimensions. The desired additional measurement of a pertinent length scale can be achieved by introducing phase measurements along with amplitude. Hydraulic conductivity controls the ability to flush unwanted fluid contaminants from the surface. Thus, inexpensive maps of hydraulic conductivity would improve planning strategies for subsequent remediation efforts. Fluid permeability is also of importance for oil-field exploitation, and thus, detailed knowledge of fluid permeability distribution in three dimensions would be a useful to petroleum reservoir analysts.

Projection Optics Box

Layton C. Hale, Terry Malsbury, Russell M. Hudyma, John M. Parker
U.S. Patent 6,147,818
November 14, 2000

A projection optics box or assembly for use in an optical assembly, such as in an extreme ultraviolet lithography (EUVL) system using 10- to 14-nanometer soft x-ray photons. The box uses numerous highly reflective optics or mirrors. Each is mounted on a precision actuator, and each reflects an optical image, such as from a mask, in the EUVL system onto a point of use, such as a target or silicon wafer. The mask would have received an optical signal from a source assembly via a series of the EUVL system's highly reflective mirrors. Most of the highly reflective optics or mirrors are mounted in a housing assembly comprising a series of bulkheads whose walls have been secured together for maximum rigidity. Because of the precision actuators, the mirrors must be positioned precisely and remotely in tip, tilt, and piston (three degrees of freedom), while also providing exact constraint.

Apparatus for Coating Powders

Daniel M. Makowiecki, John A. Kerns, Craig S. Alford, Mark A. McKernan
U.S. Patent 6,149,785
November 21, 2000

A process and apparatus for coating small particles and fibers. The process involves agitating the particles or fibers to promote uniform coating, removing adsorbed gases and static charges from the particles or fibers by an initial plasma cleaning, and coating the particles or fibers with one or more coatings. A first coating is an adhesion coating, and subsequent coatings are deposited in situ to prevent contamination at layer interfaces. The first coating is of an adhesion-forming element (tungsten, zirconium, rhenium, chromium, titanium) that is 10 to 10,000 nanometers thick. The second or final coating is composed of multiple materials from 0.1 to 10 micrometers thick, which could be, for example, of copper or silver for brazing processes or of other desired materials that define the new surface-related properties of the particles. An essential feature of the coating process is the capability to deposit in situ without interruption so that a contaminated interface that could adversely affect the coating adhesion is not formed. The process may include screening of the material to be coated and either continuous or intermittent vibration to prevent agglomeration of the material to be coated.

Defect-Tolerant Transmission Lithography Mask

Stephen P. Vernon
U.S. Patent 6,150,060
November 21, 2000

A transmission lithography mask that uses a transparent substrate or a partially transparent membrane as the active region of the mask. A reflective single-layer or multilayer coating is deposited on the membrane surface facing the illumination system. The coating is selectively patterned (removed) to form transmissive (bright) regions. Structural imperfections and defects in the coating have a negligible effect on the aerial image of the mask master pattern because the coating is used to reflect radiation out of the entrance pupil of the imaging system. Similarly, structural imperfections in the clear regions of the membrane have little influence on the amplitude or phase of the transmitted electromagnetic fields. Because the mask discards, rather than absorbs, unwanted radiation, it has reduced optical absorption and reduced thermal loading compared with those in conventional designs. For extreme ultraviolet applications, the mask circumvents the phase defect problem and is independent of the thermal loading during exposure.

Laser Machining of Explosives

Michael D. Perry, Brent C. Stuart, Paul S. Banks, Booth R. Myers, Joseph A. Sefcik
U.S. Patent 6,150,630
November 21, 2000

The invention consists of a method for machining (cutting, drilling, sculpting) explosives. By using laser pulses of a duration from 5 femtoseconds to 50 picoseconds, extremely precise and rapid machining can be achieved with essentially no heat or shock effects. The material is in essence converted from its initial solid state directly into a fully ionized plasma on a time scale too short for thermal equilibrium to be established with the lattice. As a result, heat conduction beyond the region removed is negligible, resulting in a negligible thermal stress or shock to the material beyond a few micrometers from the laser-machined surface. Hydrodynamic expansion of the plasma eliminates the need for any ancillary techniques to remove material and produces extremely high-quality machined surfaces. The explosive does not detonate or deflagrate in the process, and the material that is removed is rendered inert.

Extended-Length Microchannels for High-Density, High-Throughput Electrophoresis Systems

James C. Davidson, Joseph W. Balch
U.S. Patent 6,153,076
November 28, 2000

High-throughput electrophoresis systems that provide extended well-to-read distances on smaller substrates, thus compacting the overall systems. The electrophoresis systems use a high-density array of microchannels for electrophoresis analysis with extended read lengths. The microchannel geometry can be used individually or in conjunction with others to increase the effective length of a separation channel while minimally affecting the packing density of channels. One embodiment uses sinusoidal microchannels while another embodiment uses plural microchannels interconnected by a via. The extended channel systems can be applied to virtually any type of channel-confined chromatography.

Titanium–Chromium–Aluminum–Oxygen Thin-Film Resistors

Alan F. Jankowski, Anthony P. Schmid
U.S. Patent 6,154,119
November 28, 2000

Thin films of titanium–chromium–aluminum–oxygen (Ti–Cr–Al–O) are used as a resistor material. The films are radiofrequency-sputter-deposited from ceramic targets using a reactive working gas mixture of argon and oxygen. Resistivity values from 10 thousand to 10 million ohm-centimeters have been measured for Ti–Cr–Al–O film less than 1 micrometer thick. The film resistivity can be discretely selected through control of the target composition and the deposition parameters. The application of Ti–Cr–Al–O as a thin-film resistor has been found to be thermodynamically stable, unlike other metal-oxide films. The Ti–Cr–Al–O film can be used as a vertical or lateral resistor (for example, as a layer beneath a field-emission cathode in a flat-panel display) or as a means of controlling surface emissivity (for example, as a coating on an insulating material such as vertical wall supports in flat-panel displays).

Waveguide Detection of Right-Angle-Scattered Light in Flow Cytometry

Raymond P. Mariella, Jr.
U.S. Patent 6,154,276
November 28, 2000

A transparent flow cell is used as an index-guided optical waveguide. A detector for the flow cell (but not for the liquid stream) detects the right-angle-scattered (RAS) light exiting from one end of the flow cell. The detector(s) could view the trapped RAS light from the flow cell either directly or through intermediate optical light guides. If the light exits one end of the flow cell, then the other end of the flow cell can be given a high-reflectivity coating to approximately double the amount of light collected. This system is more robust in its alignment than the traditional flow-cytometry systems that use imaging optics, such as microscope objectives.

Method of Producing Optical-Quality Glass Having a Selected Refractive Index

John F. Poco, Lawrence W. Hrubesh
U.S. Patent 6,158,244
December 12, 2000
Optical-quality glass having a selected refractive index is produced by a two-stage drying process. A gel is produced using sol-gel chemistry techniques and first dried by controlled evaporation until the gel volume reaches a preselected value. The preselected volume determines the density and refractive index of the finally dried gel. The gel is refilled with solvent in a saturated vapor environment and then dried again by supercritical extraction of the solvent to form a glass. The glass has a refractive index less than that of the full density of glass. The range of achievable refractive indexes depends on the composition of the glass. Glasses having different refractive indexes chosen from an uninterrupted range of values can be produced from a single precursor solution.

Hollow Lensing Duct

Raymond J. Beach, Eric C. Honea, Camille Bibeau, Scott Mitchell, John Lang, Dennis Maderas, Joel Speth, Stephen A. Payne
U.S. Patent 6,160,934
December 12, 2000
A hollow-lensing-duct method of condensing (intensifying) light that combines focusing using a spherical or cylindrical lens followed by reflective waveguiding. The hollow duct tapers down from a wide input side to a narrow output side, with the input side consisting of a lens that may be coated with an antireflective coating for more efficient transmission into the duct. The inside surfaces of the hollow lens duct are appropriately coated to be reflective, preventing light from escaping by reflection as it travels along the duct (reflective waveguiding). The hollow duct has various applications for intensifying light, such as in the coupling of diode-array-pumped light to solid-state lasing materials.

In Situ Microbial Filter Used for Bioremediation

M. Leslie Carman, Robert T. Taylor
U.S. Patent 6,165,356
December 26, 2000
An improved method for in situ microbial filter bioremediation that increases the operational longevity of an in situ microbial filter emplaced into an aquifer. A method for generating a microbial filter of sufficient catalytic density and thickness, which has an increased replenishment interval, improved bacteria attachment and detachment characteristics, and endogenous stability under in situ conditions. A system for in situ water remediation.

Integrated Titer Plate-Injector Head for Microdrop Array Preparation, Storage, and Transfer

Stefan P. Swierkowski
U.S. Patent 6,165,417
December 26, 2000
An integrated titer plate-injector head for preparing and storing two-dimensional (2D) arrays of microdrops and for ejecting some or all of the microdrops and inserting them into 2D arrays of deposition sites with micrometer precision. The titer plate-injector head includes integrated precision-formed nozzles with appropriate hydrophobic surface features and evaporative constraints. A reusable pressure head with a pressure equalizing feature is added to the titer plate to perform simultaneous precision sample ejection. The titer plate-injector head may be used in various applications, including capillary electrophoresis, chemical flow injection analysis, and microsample array preparation.

Thermal Lens Elimination by Gradient-Reduced Zone Coupling of Optical Beams

Ralph H. Page, Raymond J. Beach
U.S. Patent 6,167,069
December 26, 2000
A thermal-gradient-reduced zone laser that includes a laser medium and an optically transparent plate with an index of refraction that is less than the index of refraction of the laser medium. The pump face of the laser medium is bonded to a surface of the optically transparent member. Pump light is directed through the transparent plate to optically pump the solid-state laser medium. Heat conduction is mainly through the surface of the laser medium, where the heat is introduced by the pump light. Heat flows in a direction opposite that of the pump light because the side of the laser medium that is opposite the pump face is not in thermal contact with a conductor; thus, there is no heat flux (and no temperature gradient), and a thermal-gradient-reduced zone is produced. A laser cavity is formed around the laser medium such that laser light oscillating within the laser cavity reflects by total internal reflection from the interface between the pump face and the optically transparent plate and enters and exits through a thermal-gradient-reduced zone.

Method of Casting Patterned Dielectric Structures

John F. Poco, Lawrence W. Hrubesh
U.S. Patent 6,168,737 B1
January 2, 2001
A pattern of dielectric structures is formed directly on a substrate in a single step using sol-gel chemistry and molding procedures. The resulting dielectric structures are useful in vacuum applications for electronic devices. Porous, lightweight structures having a high aspect ratio that are suitable for use as spacers between the faceplate and baseplate of a field emission display can be manufactured using this method.

Optical Coherence Domain Reflectometry Guidewire

Billy W. Colston, Matthew Everett, Luiz B. Da Silva, Dennis Matthews

U.S. Patent 6,175,669 B1

January 16, 2001

A guidewire with optical-sensing capabilities is based on a multiplexed optical coherence domain reflectometer, which allows it to sense location, thickness, and structure of the arterial walls or other intracavity regions as it travels through the body during minimally invasive medical procedures. This information will be used both to direct the guidewire through the body by detecting vascular junctions and to evaluate the nearby tissue. The guidewire contains multiple optical fibers that couple light from the proximal to distal end. Light from the fibers at the distal end of the guidewire is directed onto interior cavity walls via small-diameter optics such as gradient-index lenses and mirrored corner cubes. Both forward-viewing and side-viewing fibers can be included. The light reflected or scattered from the cavity walls is then collected by the fibers, which are multiplexed at the proximal end of the sample arm of an optical low-coherence reflectometer. The guidewire can also be used in nonmedical applications.

Use of Earth Field Spin Echo NMR to Search for Liquid Minerals

Wolfgang Stoeffl

U.S. Patent 6,177,794 B1

January 23, 2001

An instrument for measuring the spatial, qualitative, and quantitative parameters of an underground liquid mineral deposit, including oil and water, the atomic nuclei of which are nuclear-magnetic-resonance (NMR) active. A phased array of excitation and receiver antennas on the surface and/or in a borehole excites the NMR-active nuclei in the deposit, and known techniques from magnetic resonance imaging (MRI) are used to measure the spatial and quantitative distribution of the deposit. For example, a surface array consisting of four wire loops 50 to 500 meters in diameter is laid on the surface of the ground, and a weak (1.5- to 2.5-kilohertz) alternating current (ac) is applied to the array. The ac field matches the NMR frequency of hydrogen when that element is in a rather flat and uniform earth magnet field. By applying direct current to the wire loops, an additional gradient field can be generated for a few seconds and superimposed on the earth field, thus enhancing the position sensitivity of the spin echo and suppressing large surface-water signals by shifting them to a different frequency. The surface-coil excitation can be combined with downhole receivers, which are much more radio-quiet than surface receivers, to significantly enhance the position resolution of the MRI. The receiver module may include more than one receiver unit for improved penetration and better position resolution.

Inspection of Lithographic Mask Blanks for Defects

Gary E. Sommargren

U.S. Patent 6,177,993 B1

January 23, 2001

A visible-light method for detecting defects smaller than 100 nanometers on mask blanks used for lithography. Scattered light can be detected with optical heterodyne techniques more easily than with standard intensity detection methods. This invention is useful for inspecting highly polished surfaces for isolated surface defects or particulate contamination and for inspecting lithographic mask or reticule blanks for surface defects, bulk defects, or surface particulate contamination.

Dental Optical Coherence Domain Reflectometry Explorer

Matthew J. Everett, Billy W. Colston, Jr., Ujwal S. Sathyam, Luiz B. Da Silva

U.S. Patent 6,179,611 B1

January 30, 2001

This handheld, fiber-optic-based device with optical-coherence-domain-reflectometry sensing capabilities provides a profile of optical scattering as a function of depth in the tissue at the point where the tip of the dental explorer touches the tissue. This system provides information on the internal structure of the dental tissue, which is then used to detect caries and periodontal disease. Profiles of optical scattering or tissue microstructure are generated by moving the explorer across the tooth or other tissue. The profiles are combined to form a cross-sectional, or optical coherence tomography, image.

Awards

MicroDesign Resources' *Microprocessor Report*, a respected computer industry analysis newsletter, has named **extreme ultraviolet lithography** (EUVL) its **technology of the year**. The award recognizes the importance of EUVL technology to the rapidly increasing speed at which supercomputers can process increasingly large amounts of data.

According to Don Sweeney, leader of Livermore's contributions to the Virtual National Laboratory (VNL), "This award is very important within the industry. There is only one given per year." VNL is the consortium of Lawrence Livermore, Los Alamos, and Sandia national laboratories that developed this next-generation method of microchip lithography.

Funding for developing EUVL technology has come from the private sector. Intel, Advanced Micro Devices, Motorola, Micron Technology, and Germany's Infineon Techologie AG have created the limited liability company, EUV LLC, a cooperative research and development agreement, to back the project. IBM joined the consortium in March 2001. Other integrated circuit manufacturing companies, whose livelihoods depend on emerging technologies, are expected to add their support soon.

For more information about EUVL, see *S&TR*, October 1999, pp. 12–13, and November 1999, pp. 4–9, and the Lawrence Livermore EUVL Web site at lasers.llnl.gov/lasers/IST/euvl.html.

A team from the Laboratory's Medical Technology Program has won two awards for developing an implantable device to monitor glucose levels in diabetes patients: the Department of Energy's **Bright Light Award** and a Federal Laboratory Consortium (FLC) **Excellence in Technology Transfer Award**. The team includes leader **Stephen Lane, Tom Peyser, Chris Darrow, Natasha Zaitseva, Joe Satcher,** and **Doug Cary**. **Kevin O'Brien** and **Connie Pitcock** from the Laboratory's Industrial Partnerships and Commercialization Office facilitated the collaboration with and the transfer of technology to MiniMed Inc. of Sylmar, California, that brought the FLC award.

The Livermore team has been working for more than five years on a glucose monitoring technology that would be integrated with an insulin delivery device developed by MiniMed. The device is embedded under patients' skin to monitor glucose levels in the blood. The sensor would signal an insulin pump to administer insulin, when needed, to control glucose level.

The Bright Light Award honors discoveries and innovations from the DOE complex that benefit the American public, contribute to U.S. competitiveness in the global marketplace, and have the potential for significant growth. The Livermore team and four other research groups received Bright Light awards at a White House ceremony in mid-January.

The Excellence in Technology Transfer Award recognizes individuals and teams at federal laboratories for uncommon creativity and initiative in transferring to the private sector an advanced technology that significantly benefits industry, state and local government, and/or the general public.

Bruce T. Goodwin, B Division leader in the Laboratory's Defense and Nuclear Technologies Directorate, has been selected to receive one of ***Aviation Week & Space Technology*** magazine's **Aerospace Laurels**. For the past 44 years, these awards have honored individuals and teams that have made significant contributions to the global field of aerospace. Goodwin's award is in the category of Government/Military. He was named, along with C. Paul Robinson, president of Sandia National Laboratories, and H. Terry Hawkins, director of the Nonproliferation and International Security Division at Los Alamos National Laboratory, "for public warnings about risks to the viability of the U.S. nuclear weapons stockpile, deterioration of the nation's nuclear intelligence infrastructure, and losses of weapons-design intellectual resources from the laboratories." At great risk to their careers, these laboratory scientists and leaders resisted attempts to silence them, ensuring that Congress and the public became aware of critical nuclear-related national security problems.

Abstract

A New Kind of Biological Research

Lawrence Livermore's Computational Biology Group is linking advanced computer simulations to laboratory experiments. The result is new explanations of biological phenomena at an unprecedented level of detail. The simulations provide a "virtual microscope" that combines powerful computers with software programs and applies them to the structures and energetics of biological molecules. The most advanced form of the simulations, called first-principles molecular dynamics, uses quantum mechanical forces to simulate biochemical processes. The simulations often run on Livermore's teraops (trillion operations per second) supercomputers, some of the most powerful in the world. The Computational Biology Group is involved in a wide range of projects that includes studies of the action of anticancer drugs, the DNA-binding properties of food mutagens, the mechanisms of DNA repair enzymes, and the biophysics of DNA base pairing.

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Uncovering Hidden Defects with Neutrons

Livermore scientists are making advances in the use of high-energy neutrons to image the internal structures of thick objects. Neutron imaging will be an important supplement to x-ray imaging for the nondestructive evaluation of stockpiled nuclear weapons.

Also in May

- *What the mouse genome reveals about the human genome.*
- *The new Contained Firing Facility at Livermore's Site 300 is the largest explosives chamber in the world.*
- *The National Ignition Facility's target chamber is ready to be fitted with research systems and instrumentation.*

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